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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,832	CHOW ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-18,20,24,25 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/9/2005 has been entered.

3. The amendment filed on 11/09/2004 has been entered.

4. Claims 2-14, 19, 21-23 and 26 have been cancelled and new claims 28-31 have been added.

5. Claims 1, 15-18, 20, 24-25 and 27-31 are under consideration.

Double Patenting

6. Claims 1, 15-18, 20, 24-25 and 27-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/498450 (US Patent Publication no 20050220772). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a method of treating or preventing HIV infection by transplanting stem cells having a beneficial gene. For example, claim 1 of instant application encompasses a method for preventing or treating HIV infection in humans by transplanting stem cell rich population of cell that has beneficial gene that is polymorphism in CCR5 gene. Claims 15-17 depend on method of claim 1 wherein polymorphism is either a 32-basepair deletions in coding region or CCR5m303 or in promoter region. Claim 18 depends on method of claim 1 wherein stem cell population will be selected from bone marrow, peripheral blood, umbilical cord blood and adipose tissue. Remaining claims are directed to screen cell sample from human donor to identify stem cell population having beneficial gene and identification of HLA genotype or phenotype. Whereas, Claim 1 of the application No. 10/498450 is directed to a method of treating or preventing HIV infection in humans by screening plurality of cells to identify stem cells having beneficial gene and then transplanting stem cell with beneficial gene into HIV infected patients. The remaining claims 2-33 encompass all the limitations of instant application. Thus, the claims of application no 10/498450 (US Patent publication no 20050220772) differ only with respect to broader

scope of beneficial genes that could be used in the method for treating or preventing HIV infection, which encompasses polymorphism in CCR5 specifically claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 15-18, 20, 24-25 and 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the previous office action dated 2/12/2004, 11/2/2204 and, as discussed further in this office action. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 encompasses a method of preventing or treating HIV infection in a human by transplanting a stem cell rich population of cells obtained from a human donor having beneficial gene that is a polymorphism in a CCR5 gene. Claims 15-17 depend on method claim 1 wherein polymorphism is either a 32-basepair deletions in coding region or CCR5m303 or in promoter region. Claim 18 depend on method of claim 1 wherein steam cell population will be selected from bone marrow, peripheral blood, umbilical cord blood and adipose tissue. Claim 20 describes the method of transplanting a stem cell rich population further comprises identification of the HLA genotype or phenotype of stem cell rich population. Claims 24-25 encompass method of screening cell sample from human donor to identify the stem cell rich population of the cell that has polymorphism in CCR5 gene by different techniques. Claims 27-31 encompass stem cell rich population of cells are from umbilical cord blood subsequent claims disclose a method-comprising identification of HLA genotype via high throughput such that genotype or phenotype of such cell is compatible with HLA genotype or phenotype of human.

The application as filed is not enabling for the invention because art of **preventing** or treating HIV by transplanting a stem cell rich population of cells obtained from a human donor having any beneficial gene was unpredictable as has been recognized by the art of skill and therefore require undue experimentation. As will be shown below, these aspects as well as limitations were not enabled for the claimed invention at the time of filling of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled commensurate with the full scope of the claims.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claims 1, 15-18, 20, 24-25 and 27-31 are broad in scope. The following paragraph will outline the full scope of the claims:

Claimed invention recites a method of preventing or treating HIV infection in human by transplanting a stem cell rich population of cells having a beneficial gene that is a polymorphism in a CCR5 gene. Since these claims encompass infection from any strain of HIV and transplanting any stem cell rich population subsequently limiting to few, any mutation in any part of the gene subsequently limiting to either promoter or coding region of CCR5. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of these, aspect must be shown to a reasonable extent so that one of the ordinary skills in the art would be able to practice the invention without any undue burden being on such Artisan.

The specification as filed provides a general description of polymorphisms of genes encoding ligand for the co receptor CCR5 and CXCR4 that confer resistance to HIV (pp 1). The specification also states that HLA alleles influence HIV-1 disease progression (refer pp 1-2). Remaining specification discloses definition of terms, general description of biological method, method of stem cell transplant and HLA genotyping.

Furthermore, it is noted that application as filed itself states "the discovery of the fact that certain polymorphism confer resistance to HIV has led to **proposal** of therapies which repopulate the immune system with cells that could confer resistance to HIV infection". The specification also states, "nature of such therapies **should** reduce side effect" suggesting that treatment or prevention against HIV infection by transplanting stem or any other cell to confer resistance to HIV infection was just a **theory** that was not reduced to practice at the time of filing of this application as neither art nor specification specifically teaches how stem cell having beneficial gene that is polymorphism in a CCR5 gene would have prevented or treated HIV infection. In summary, the specification does not provide any specific guidance for the claimed invention because the specification as filed does not teach how to many stem cells would be enough to confer resistance in a subject already infected with any strain of HIV as compare to a normal healthy individual for prevention of HIV infection.

The method of treating or preventing HIV infection by transplanting stem cell derived from human was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions. Given this lack of reasonable predictability in specification and the art, the Artisan would require a large amount of information from Applicant's **examples** to provide the guidance to provide reasonable predictability.

Applicant example only provides a **schematic** of proposed therapy in human without disclosing any specific. In addition Applicant do not provide any disclosure on how stem cell deficient in CCR5 delta 32 will be grown *ex vivo* or *in vivo*. Furthermore, it

is not enough to reasonably predict that the stem cell rich population with CCR5 polymorphism administrated at reasonable level for appropriate time duration in human would be efficacious in treating or preventing HIV infection. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in human with all HIV variant. An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of stem cell transplant in HIV infection was **not routine** rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Claims 1, 15-18, 20 and 27-31 require stem cell rich population of cells from any human donor having beneficial gene that is polymorphism in a CCR5 gene. However, art of record shows that beneficial gene is not present uniformaly in human population. For example, Lucotte (Hum Immunol. 2001: 62(9):933-6; and references therein) discloses the allelic frequency of 32 basepair deletion is very rarely seen in African population and only 10% population of European desent are homozygous for 32 basepair deletion, which only partially protects against HIV infection (pp 933, right column, lines 1-6). It is also not apparent how skilled artisan without any undue experimentation, practices method as contemplated by the instant claims particularly given the unpredictability of growing stem cell deficient in CCR5 delta 32 *ex vivo* or *in vitro* and unpredictability expressed in the art and discussed in this and previous office actions dated 2/12/04 and 11/2/04. Shih et al (J Hematother Stem Cell Res. 2000, 9(5):

621-628) state, "increasing means for identifying and purifying hematopoietic stem cells and cytokines have facilitated and improved the development of ex vivo stem cell expansion technology. However, technology has **not yet** reached a stage where **ex vivo**-expanded hematopoietic progenitors and stem cells can be used routinely for replacement therapy (abstract). Thus, an artisan would require undue experimentation to practice the claimed inventions.

At the time of the invention, the art teaches beneficial effects of HIV co-receptor CCR5 polymorphism in HIV infected patients in disease progression (McDermott et al Lancet 352: 866-870, 1998). However, prior and post filing arts do not teach how an artisan would treat or prevent infection with different strains of HIV in patients by transplanting stem cells that have the protective polymorphism. There were contradictory reports that in certain instance CCR5 polymorphism did not provide any resistance to the HIV infection (Roman et al., 2002, HIV Clinical Trials 3: 195-201, pp 195, column 2, paragraph1 bridging to 196).

In addition, Naif et al (Journal of Virology, 2002, 72(1): 3114-3124) demonstrates the ability of certain strains of HIV to readily use CXCR4 for infection or entry into macrophages, which is highly relevant to the pathogenesis of late-stage disease and presumably also HIV transmission (abstract). Naif et al show that a primary HIV isolate from an HIV-infected **CCR5-deficient person** can infect **both macrophages** and **T-cell** lines via the co receptor CXCR4. Furthermore, Sheppard et al (Journal of acquired Immune Deficiency Syndrome, 29: 307-313) disclose that delta 32 mediated resistance to HIV are incomplete and is associated with acquisition of exclusively-X4 variants of

HIV-1 (abstract, pp311). In addition, it is emphasized that Sheppard et al state " further studies are needed to explore the relationship between pattern of co receptor usage and mechanism of pathogenesis (pp312, column 2, paragraph 2). Reeves et al (Journal of General Virology, 2002, 83, 1253-1265, and references therein) states "in contrast to HIV-1, some HIV-2 strains are able to infect PBMCs independently of either CCR5 or CXCR4 implicating a potential role of at least some alternative receptor(s) for infection *in vivo*. Additionally, HIV-2 infection may result in higher levels of β-chemokine production compared to HIV-1 infection and may thus drive evolution of alternative receptor use (pp 1257, paragraph 1)". This in conjunction with Dean and O'Brien (1997) as discussed in previous non final and Final office action (dated 11/2/2004) clearly establishes the unpredictability of treating preventing or treating HIV infection (including different variant) by transplanting stem cell having beneficial gene that has polymorphism in CCR5 gene. The specification does not provide sufficient guidance to overcome this unpredictability for practicing the claimed method in-patient infected with different strains of HIV. The specification does not provide any guidance as to how would an artisan select which polymorphism will be beneficial for different strain of viruses. Therefore, at the time of the invention there was no evidence of treating or preventing HIV infection in humans by transplanting stem cells with any beneficial gene having polymorphism and treatment or prevention of a HIV infection would have been unpredictable since a number of factors played role in the process of blocking infection as shown by the art of record.

Specification also does not provide disclosure on **number of stem cell** that are required to be transplanted to **elicit specific protective response**. It is also not apparent how an artisan would grow **enough** of plurality of stem cell rich population that is **sufficient** for the prevention or treatment of HIV infection. In absence of such guidance, an artisan of the skill of the art would have to perform undue experimentation to grow enough of different type of stem cells and determine the precise amount of therapeutic composition required to a HIV infected individuals. Although much will be dependent upon the specific requirement of the patient, however, without any specific guidance on how many stem cells should be transplanted in order achieve desired therapeutic response the method as claimed will not be enabling for the use in humans.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior arts do not teach a method of treating or preventing HIV infection in human by transplanting stem cell population having a beneficial gene that is polymorphism in CCR5 gene in humans. An artisan of skill would have required **undue** experimentation to practice the invention because the art of ex *vivo* cell therapy for the treatment or prevention of HIV in general was unpredictable at the time of filling of this application as supported by the observations in the art record.

Response to Arguments

6. Applicant arguments filled on 11/5/2005 have been fully considered but they are not persuasive. Applicant in their appeal brief on page 6, last paragraph argue that the specification teaches the sources of stem cell rich population (at pages 7, lines 23-25 and page 9, lines 21-25). In response, it is noted that the indicated section of the specification is a general description and does not describe any specific guidance. Such a general description is not sufficient to provide enabling support because claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to expand stem cell **ex vivo** and in vivo in order to attain therapeutic response. The disclosure in the specification does not provide any specific guidance to an artisan how to **isolate** the stem cells with a beneficial gene and expand them **ex vivo** or **in vivo** in an amount **sufficient** for transplantation as stated in previous non-Final and Final office actions. These would have required undue experimentation because neither the specification nor the art of record teaches specific guidance and a method of treating HIV infection. At the time of filing of this application, *ex vivo* expansion of hematopoietic stem and progenitor cells in general was unpredictable and it was not **routine** in the art to *in vivo* expand stem cells for transplantation in patient (Srour et al The Journal of Hematotherapy 8:93-102, 1999, particularly, pp97). Since in the instant case the stem cells will have a particular mutation in a receptor or co-receptor gene, and it is required in large enough quantity to support the treatment and or prevention against HIV infection. It is not clear from the specification what would be the culture conditions that would be required to expand and

maintain the stem cells *in vitro or ex vivo*. It is noted that while the art and specification teaches that CCR5 delta 32 mutant may make a cell resistant to HIV infection. It does not provide any guidance for culturing and maintaining a stem cell expressing the mutant CCR5 and it is unpredictable whether such a stem cell would be viable *in vitro* and what would be the role of a mutant gene in the survival of the cell *in vivo* or *ex vivo*.

On page 7, in the second paragraph, applicant argue that they satisfy the enablement requirement as bone marrow transplantation to person with HIV infection was practiced at the time of filing and did not require undue experimentation. The applicant provides the reference of Levine et al (Hematology, Hematology, 2001,463-478) to support the notion of bone marrow transplant. In response, it is noted that the article by Levine et al primarily describe autologous stem cell transplant for HIV infected patient with high-risk lymphoma. The therapeutic effectiveness of bone marrow transplant in lymphoma is well documented in art; however, these finding cannot be extrapolated to instantly claim stem cell transplantation in HIV infected individual. In fact, Levine et al (2001) state "hematologically based therapies using gene modified cell or ***ex vivo*** generated cells offer a **possible** approach" (pp 466, column 1, paragraph 3). This suggests that art of immune regeneration by transplanting *ex vivo* generated cell for the treatment of HIV infection was **not routine**, just a **hypothesis** at the time of filing of this application and an artisan would have to perform undue experimentation to practice the claimed methods.

On page 8, in the third paragraph, applicant argues that O'Brien article was written in 1997 and author did not appreciate the differences between M and T tropic

HIV virus. In response, applicants are directed to claim 1 and other claims that depend from claim 1, as instantly present, these claims encompass **all strains** and **variants** of the HIV including HIV-2, M and **T tropic** as discussed earlier in this office action.

On page 9, in the third paragraph applicants have argued that the therapeutic benefit outweighs the presence of residual endogenous infected cell population after the radiation and chemotherapy is not persuasive. Applicants argument that hematopoietic cancer patients also routinely receive bone marrow transplant with some risk of cancer cell remaining in the system and benefit of such a treatment outweigh the risk. The argument that currently no viable therapeutic option is available for treating or preventing HIV and thus benefit from instantly claimed therapy outweighs the risk of infection is irrelevant. The real question is whether an artisan of skill could actually practice the invention based on the disclosure in this application. Furthermore, efficacy and positive outcome of treatment of hematopoietic cancer with bone marrow transplant is well documented in the art and thus, some risk in an effective treatment is expected. However, in the instant application, neither specification nor art of record provide any guidance that instantly claimed method of treatment or prevention of HIV would be efficacious as discussed in previous office actions dated 2/12/2004 and 11/2/2204. It is emphasized that in absence of any working example or evidence from the art of record an artisan would require **undue experimentation** to determine whether the instantly claimed methods would be effective against different strains of HIV before suggesting patients benefit of such a therapy outweighs the risk as argued by the applicant.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh, Ph.D.
Examiner, AU 1632